Final Research Project

First trimester maternal level of PAPP-A, βhCG and ethnicity as predictive of Intrauterine Growth Restriction

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ABSTRACT

Background: *Intrauterine growth restriction (IUGR) is one of the leading causes of perinatal mortality and morbidity. Nowadays, this condition is detected in the 3rt and last trimester of gestation when the pathology is already established and success of therapeutic strategies are limited.*

As the physiopathology of the disease suggests that the problem stems from poor placental implantation, it would be quite advantageous to identify women at increased risk in the first or second trimester of gestation because it then might be possible to offer treatment interventions or at least to establish increased surveillance for high risk pregnancies. Maternal levels of pregnancy-associated plasma protein-A (PAPP-A) and free β human chorionic gonadotropin (free βhCG) has been shown to be effective in first trimester screening for chromosomal abnormalities, primarily trisomies 21, 13 and 18. Previous studies evaluating PAPP-A and free βhCG measured in the first trimester in relation with IUGR have provided conflicting results. Moreover, it has been suggested that black ethnicity is another important predictive factor for fetal growth restriction.

Objective: *To analyse the association between first trimester serum analytes (PAPP-A and free βhCG) and ethnicity with Intrauterine Growth Restriction.*

Methods: *The study consists in a retrospective cohort, including all singleton pregnancies with complete outcome data that had undergone first trimester screening (PAPP-A and free βhCG) at 11-13^{+6}weeks of gestation between 1/1/2010 - 31/12/2012 in Hospital Universitari Dr Josep Trueta. Biochemical markers are converted to multiples of the median (MoMs) and percentiles 5 and 10 are calculated. The association between free βhCG and PAPP-A with the incidence of IUGR is evaluated in combination with maternal ethnicity. Bivariate and logistic regression analyses are performed to adjust this association for co variables.*

1 INTRODUCTION

1.1 Intrauterine growth restriction (IUGR)

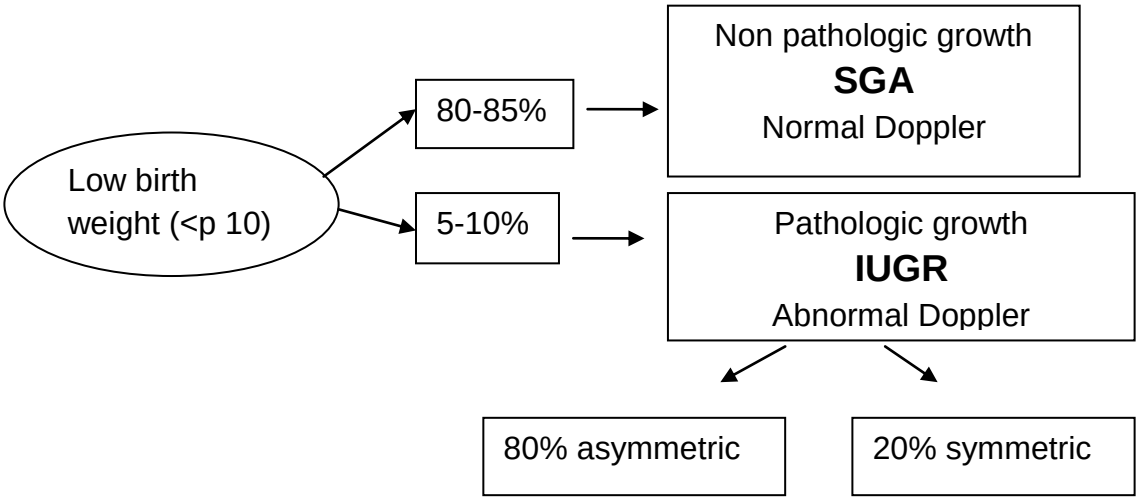
1.1.1 HISTORY

The terminology used to describe abnormal fetal growth is inconsistent and confusing. The first references carried in medical literature concerning low birthweight babies refer to 1919 when “premature” was defined as the newborn weighing less than 2.500 gram. Afterwards, in 1961 the World Health Organisation (WHO) acknowledged that many babies defined as premature were not born early on time but they are newborns with “low weight” at born. The current WHO criteria for low birth weight are a weight less than 2,500 g or below the 10th percentile for gestational age. (1)

1.1.2 CONCEPT

Intrauterine growth restriction (IUGR) is defined as an **estimated weight below the 10th percentile for the gestational age**. It is a dynamic term that implies a pathological process in which one or more factors inhibit the pre-programmed genetic growth potential and where Doppler Ultrasound is abnormal (2)

By contrast, the concept of small for gestational age (SGA) is purely statistical and it is a static term. Include all **newborns which weight is below the 10th percentile** with normal Doppler Ultrasound (2)



This distinction is important because newborns with a prenatal diagnosis of IUGR have more perinatal morbidity than neonates who meet the criteria for diagnosis of SGA, but have an otherwise healthy in-utero environment.(2) IUGR will be the base of this study.

1.1.3 EPIDEMIOLOGY AND RELEVANCE

Fetal growth restriction is the second leading cause of perinatal morbidity and mortality, followed only by prematurity (3). The prevalence of IUGR is estimated to be approximately 5% in the general obstetric population. (4) However, the incidence varies depending on the geographic location and the standard growth curves used as reference (5) According to the "Instituto Nacional de Estadística" (INE) the prevalence of newborns weighing less than 2500g in Spain during 2012 was 7'77% –Picture I– Neonates with low birth weight at term have a perinatal mortality rate that is 5 to 30 times higher than the ones who are in the 50th percentile. The rate increases to 70-100 times higher when the weigh is less than 1500g (5) Infants with IUGR are between 1.6 and 12 times more likely to develop a complication (low Apgar score, hypoglycemia, hypothermia, apnea, respiratory distress and fetal asphyxia) than infants with an adequate ponderal index.(6)

Moreover, a worse neurological and cognitive development is assumed to them (7).

1.1.4 CLASSIFICATION AND ETIOLOGY

- According to time of establishment: early (<28th week) or late (>28th week)
- According to fetal body proportions (8):
  - **Symmetric (type I)** → 20% of IUGR. Growth pattern in which both cranial and abdomen perimeters are proportionally decreased and it is caused by an alteration in the cellular hyperplasia phase in all fetal organs during the first gestational trimester. The main causes are chromosomal aneuploidies and early congenital infections. The fetal morbility and mortality rates are higher in this type of IUGR.
  - **Asymmetric (type II)** → 70-80% of IUGR. There is a larger decrease in the abdomen perimeter than in the cranial one. When there is not an evident explanation of this situation (i.e. maternal hypertension, infection, etc) the main cause is an uteroplacental vascular insufficiency, and they start to present signs of decreased growth in the 3rt gestational trimester. This condition is the main objective of the current study.

Etiology of IUGR

MATERNAL	FETAL/PLACENTA
- Pathologies: chronic hypertension, pre-gestational diabetes, collagen vascular disease (i.e renal disease, Crohn's disease, systemic lupus erythematosus, etc.) - Teratogens and toxics: anticonvulsants, methotrexate, warfarin, alcohol, smoking, drugs. - Poor maternal weigh gain and nutrition - Extreme maternal age (< 16y or > 35y).	Uteroplacental vascular insufficiency Congenital infections (TORCH) Aneuploidies (trisomy 21, 13,18 and Turner syndrome) Discordant growth in multiple gestation Congenital malformations

Asymmetric IUGR is classified in 5 grades according to severity of the vascular insufficiency evaluated by Doppler ultrasound:

1) No suggestive signs of placental insufficiency
2) Moderate increase in placental resistance without signs of redistribution (umbilical artery PI> p95)
3) Severe increase in placental resistance without signs of redistribution (umbilical artery diastolic flow is absent)
4) Hemodynamic signs of redistribution (cerebral vasodilatation = middle cerebral artery PI <p 5)
5) Severe hemodynamic impairment (umbilical artery reversed flow and / or pulsatile umbilical vein and / or with ductus venosus absent or reversed flow)

1.1.5 SCREENING AND DIAGNOSIS

Screening of Asymmetric RCIU

No current screening is made for asymmetric RCIU in the first trimester of gestation.

History and physical examination→ The clinical risk of IUGR is already routinely estimated by reviewing the medical and obstetric history. Most clinical studies demonstrate that techniques such as measuring the symphysis fundal height (SFH) alone missed the diagnosis of IUGR almost half the time. (9)

Ultrasound biometry in 2nd trimester→If IUGR is suspected based on risk factors and/or clinical assessment, ultrasonography must be performed to assess fetal size and growth; it is the **"Gold Standard"** in the diagnosis of RCIU in the 3rt trimester. The measurements most commonly used are the biparietal diameter, head circumference, abdominal circumference and femur length. Percentiles have been established for each of these parameters, and fetal weight can be estimated. The most sensitive indicator of symmetric and asymmetric IUGR is the abdominal circumference, which has a sensitivity of over 95 percent if the measurement is below the 2.5th percentile.(10) Accurate dating of the pregnancy is essential in the use of any parameter. In the first trimester, the crown-rump length (CRL) is used to estimate gestational age. (11)

Amniotic fluid → A decreased volume of amniotic fluid is closely associated with IUGR as suggests a redistribution of the blood flow by placenta insufficiency. Significant morbidity has been found to exist in pregnancies with an amniotic fluid index value of less than 5 cm (12).

Doppler Ultrasound (Uterine artery, umbilical artery, middle cerebral artery) → The initial sign of feto-placental vascular insufficiency is a reduction in end-diastolic flow, reflected

by an elevated PI (pulsatility index). The disease may progress to absent end- diastolic flow, and finally to reversed end-diastolic. There is a high transplacentary resistance to the blood flow and depending on the grade of severity it will be reflected as a decrease, absence or reverse of the flow in the end of the diastole, that is to say, a persistence in the notch. In the middle cerebral artery there is a decrease of the pulsatibility and resistence index as the hypoxia on the fetus causes a redistribution of the blood flow to essential organs (brain, heart and adrenal glands). (13)

The combination of Ultrasound biometries with umbilical and middle cerebral artery Doppler in the 2nd trimester provides the best tool to identify small fetuses at risk for adverse outcome.

Neonatal diagnosis

The definitive diagnosis is made at birth by confirming the real weight and calculating the percentile for the age.

1.1.6 MANAGEMENT AND TREATMENT

The management of IUGR must be individualized for each patient. The goal is to deliver the healthiest possible infant at the optimal time. To achieve this is important to aim that continued fetal tests must be performed to monitor fetal well-being (13):

- Fetal karyotype → In symmetric RCIU with early onset in the 1rst trimester and especially in the context of an abnormal fetal anatomical ultrasound examination (documentation of fetal anomalies or soft markers associated with aneuploidy).
- Doppler studies →Enables gradation of severity considering the degree of placental disease, the level of distribution and the degree of cardiac compromise.
- Biophysical profile → Method of assessing the presence of fetal asphyxia and/or chronic hypoxia. It is based on 5 variables: fetal breathing, fetal movement, fetal muscle tone, non-stress fetal heart rate testing and semi-quantive amniotic fluid volume assessment.

Once the etiology of IUGR has been established, and the well-being of the fetus is confirmed, various investigators have evaluated potential treatment modalities in the hope of increasing birth weight and extending gestational age. The universally available therapeutic options that currently show any promise in affecting outcome are the antenatal administration of steroids in preterm pregnancies (before 34 weeks of gestation) and delivery at an institution with a neonatal care unit that is able to address the management complexities of the IUGR neonate (14). Other treatments have been evaluated in several studies such as: Maternal oxygen administration (15), additional nutrient supplement,

hospitalization for bedrest (16), calcium channel blockers (17), low dose ASA(18) and heparin(19); but only limited data prove their efficacy.

1.2 Pregnancy-associated plasma protein (PAPP-A)

1.2.1 STRUCTURE

PAPP-A is a macromolecular glycoprotein that belongs to the metzincin superfamily of metalloproteinases considered as a new family, the pappalysins. The PAPP-A gene is located in 9q33.1 human chromosome.

PAPP-A exists in pregnancy serum as a heterotetrameric 2:2 complex with 2 subunits PAPP-A fixed by disulfide bridges to 2 proMBP molecules (proform of eosinophil major basic protein). (20)

The main site of both PAPP-A and proMBP synthesis during pregnancy is the syncytiotrophoblast and is present in the maternal circulation soon after implantation and increases in concentrations throughout pregnancy (21) They are also present in several reproductive and nonreproductive tissue (i.e female reproductive tissue, kidney, colon, bone marrow cells, breast and breast carcinoma) although the levels are much lower than in the placenta. (20)

1.2.2 FUNCTION

This enzyme is unique among other multifunctional proteases capable of degrading insulin-like growth factor-binding protein-4 (IGFBP-4). IGFBP-4 is a specific protein transporter that joins IGF-1 and IGF-2 blocking their interactions with cell surface receptors. As PAPP-A splits IGFBP-4, low levels of it are associated with higher levels of IGFBP-4 and consequently with lower levels of free IGFs. (22)

The IGFs play a role in the regulation of fetal growth by controlling uptake of glucose and amino acids in trophoblast and its important in the autocrine and paracrine control of trophoblast invasion of the decidua. (23)

1.2.3 PAPP-A IN PREGNANCY

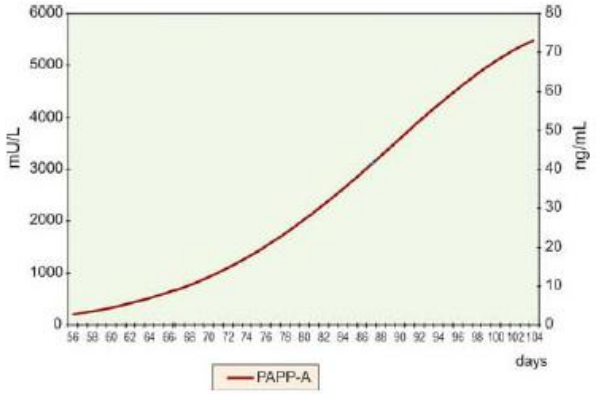


Fig 1: *Maternal serum levels of PAPP-A in 8- 15 weeks of pregnancy*

(Comas, Carmen; Rodríguez, M. Angeles; et al. Impact of ductus venosus assessment in screening Down syndrome. Donald School Journal of Ultrasound in Obstetrics & Gynecology . Apr-Jun2009, Vol. 3 Issue 2, page 12)

1.2.4 CLINICAL APPLICATIONS

Trisomy 21 (Down syndrome)

Maternal serum levels of PAPP-A in the first trimester were found significantly reduced (< 0, 4 MoM) when a fetus was affected by Down syndrome (24). In 1995 it was found that maternal levels of PAPP-A and free β human corionic gonadotropin (βhCG) used together with maternal age had a detection rate of 62% at a false positive rate of 5% (25). Later, in 1999 it was found that the most effective method of screening for chromosomal abnormalities is by a combination of fetal nuchal translucency thickness and maternal serum free βhCG and PAPP-A at 10-14 weeks of gestation. The sensitivity of this screening test is estimated as high as 90% for detecting trisomy 21, with a false positive rate of 5% (26, 27). Actually this screening test is offered to all pregnant women.

Other clinical utilities have been studied on its predictive value of detecting threatened abortion, ectopic gravidity, preeclampsia and diabetic pregnancy all of them with discouraging results. (20)

1.3 β human chorionic gonadotropin (βhCG)

1.3.1 STRUCTURE

Human chorionic gonadotropin (hCG) is a glycoproteic hormone that comprise 2 subunits, alpha and beta joined non covalently. The alpha subunit is similar in all glycoproteins (luteinising hormone-LH, follicle stimulating hormone-FSH and thyroid-stimulating hormone-TSH). On the other hand, βhCG is the determinant of his specific biological function and is produced by the syncytiotrophoblastic cells of the placenta soon after the implantation of the fertilized oocyte. (28)

1.3.2 FUNCTION

It has numerous functions. The main one is that interacts with luteinizing hormone / chroriogonadotropin receptor (LHCG) and promotes maintenance of the corpus luteum during the beginnning of pregnancy, whose function is the secretion of hormone progesterone during the first trimester. Progesterone enriches uterus with a thick lining of blood vessels and capillaries so that it can sustain fetal growth. Levels of hCG can be measured in blood or urine. Moreover, it promotes angiogenesis in uterine vasculature and promote growth of cytotrophoblast cells and the invasion as occurs in implantation.

1.3.3 βhCG IN PREGNANCY

It is present in maternal circulation immediately after implantation and raises up until 10 weeks and then declines to constant level from 20 weeks of gestation. (29)

hCG levels in weeks of pregnancy:

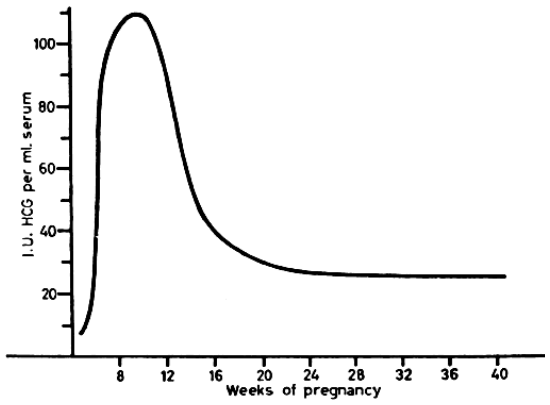


Fig 2: Serum concentration of human chorionic gonadotropin (HCG) during pregnancy.

(Danforth DN.Textbook of Obstetrics and *Gynecology. New York, Harper & Row, 1971 pag.531)*

1.3.4 CLINICAL APPLICATIONS (28)

Pregnancy testing: Determining βhCG serum levels can detect levels as low as 5mlU/ml.

Tumor marker: High levels of βhCG are associated with gestational throphoblastic tumors and testicular cancer.

Ectopic and abortion pregnancy: High levels without evidence of embryo in the uterus by ecography.

Screening of Down Syndrome: Together with levels of PAPPA, mother's age and nuchal translucency are performed at 11-13 weeks gestation and indicates the individual risk. Maternal levels of βhCG were found increased (> 2-2,5 MoM) when the fetus was affected (25).

Fertility: As ovulation inductor instead of luteinising hormone (LH) when there are one or more ovarian follicles. It occurs in 38-40 hours after hCG injection and IVF (in vitro fecundation) can be proceed.

1.4 Justification

Intrauterine growth restriction is one of the major determinants of perinatal mortality and morbidity. Actually, the diagnosis of this condition is made in the 3rt trimester when it is already established. Therefore, a major challenge for the modern obstetrics is finding the appropriate method that reports us the risk fetuses and consequently perform a closer monitoring, as it has been demonstrated that antenatal detection of SGA significantly improved outcome (30). In addition, early identification of high risk women might help to discriminate between IUGR fetuses from constitutional small-for-gestational-age (SGA) fetuses.

First trimester serum screening is nowadays used as a method of identifying fetuses at increased risk of open neural tube defects and chromosomal abnormalities (trisomy 21 and 18). Over the last years, numerous authors have studied the potential of first and second trimester maternal markers screening to identify impaired placental development and subsequent pregnancy complications. Several potent predictive markers have been studied, such as Doppler measurements, three dimensional ultrasound volume measurements and maternal serum markers. However, large and even controversial differences in screening performance are reported.

Previous studies evaluating PAPP-A and free βhCG measured in first trimester in relation to IUGR have provided conflicting results.

Low levels of both markers have constantly been reported to be associated with IUGR (31, 32, 33, 34, 35, 36, 37, 44 and 45). However, results of low βhCG were usually not statistically significant (32, 34, 35 44 and 45) except from two of them who found statistically association (31, 37). In contrast, there are other several studies reporting the absence of significant association between first trimester free βhCG and PAPP-A levels and subsequent IUGR (38, 42, and 43). Low levels of PAPP-A have more constantly been reported with IUGR although a clear level of cut-off in the definition of low PAPP-A is not determined (32, 33, 34, 35, 37, 44 and 45).

Moreover, a recent study found a positive association between high levels of βhCG (>90th percentile) and IUGR. Furthermore, the same study found a statistically significant association between African-American ethnicity and IUGR with a Relative Risk of 2, 7 (1.7-4.3) and p value= 0.001. (39)

Other studies have remarked the importance of ethnicity as an important factor to take into account at the moment of correcting levels of such markers when calculating the risk of trisomy in the first trimester screening. Significant differences were reported in levels

between Caucasian, Afro-Caribbean, Asian and Hispanic ethnicities (40, 41). No study has yet examined the relationship between markers, ethnicity and the association with Intrauterine Growth Restriction. The great cultural diversity is a relatively emerging issue in our country and is different from North America, where these studies were performed.

Moreover, all previous studies remarked (31, 32, 33, 34, 35, 36, and 37) established as definition of IUGR the birth weight under the 10^{th} percentile, without discriminating if Doppler was normal or pathologic and therefore including SGA fetuses in the study when it is not a pathologic condition.

In summary, previous studies suggest the association between low levels of PAPP-A and βhCG in the first trimester with the subsequent emerge of IUGR even though the results still show some controversy. As there is a high suspicion that ethnicity is an important factor when interpreting the results, this study will observe if there are differences between principal ethnicities in our country (Caucasian, Asiatic, Black-African, Maghreb and Others) -with normal and low levels of both biomarkers- and the development of IUGR. IUGR will be defined with the actual definition and we will focus only on pathologic growth restriction.

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2. HYPOTESIS AND OBJECTIVES OF THE WORK

OBJECTIVES

- To analyze if low levels of βhCG in the first trimester screening test are associated with intrauterine growth restriction in pregnant woman subdivided according to ethnicity (Caucasian, Asiatic, Maghreb, Black-African and others)
- To analyze whether low levels of PAPP-A in the first trimester screening test are associated with intrauterine growth restriction in pregnant woman subdivided according to ethnicity (Caucasian, Asiatic, Maghreb, Black-African and others)

HYPOTHESIS

- Intrauterine growth restriction depends on low levels of βhCG in the first trimester of gestation and ethnicity.
- Intrauterine growth restriction depends on low levels of PAPP-A in the first trimester of gestation and ethnicity.

3. MATERIAL AND METHODS

3.1 Design

This study is designed as a retrospective cohort study. From a cohort divided in five groups (Caucasian, Asiatic, Maghreb, Black-African and others) and each group subdivided in two (normal and low levels of PAPP-A or βhCG) we retrospectively compare if they developed IUGR or not in the 3rt trimester of gestation. This process will be done for levels of PAPP-A and βhCG separately.

3.2 *Population*

The study population include all women with singleton pregnancies who are excluded of major fetal abnormalities in the first trimester screening.

3.3 Inclusion and exclusion criteria (Table 1)

INCLUSION	EXCLUSION
○ Singleton pregnancies ○ Complete screening test first trimester ○ Delivery in our center ○ All data registered	○ Multiple gestation ○ Chromosomal abnormalities (T21, T18) ○ Preterm deliveries ○ Miscarriage ○ Pregnancies not ended at our center ○ Women with missing values

3.4 Sample

SAMPLING METHOD

Consecutive sampling was carried out as women were tested in the first trimester screening and then followed if they gave birth to IUGR fetuses or not.

The study sample will include all women with singleton pregnancies from 1/1/2010 to 31/12/2012 (3 years) who delivered at Hospital Universitari Dr Josep Trueta and who complied for first trimester screening for trisomy 21 and 18 by a combination of fetal nuchal translucency thickness and maternal serum free βhCG and PAPP-A at 11-13^{+6} weeks of gestation. In the Hospital Universitari Dr Josep Trueta this screening test is offered to all pregnant women since 07/2008 when the “Programa de diagnòstic prenatal d’anomalíes congènites fetals a Catalunya” was approved – Annex 1 –

POWER AND SAMPLE SIZE

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **160** exposed subjects (low levels of markers) and **480** in the non-exposed (not low levels of markers) are necessary to recognize as statistically significant a relative risk greater than or equal to **2**. A proportion in the non-exposed group has been estimated to be 0, 1. It has been anticipated a drop-out rate of 5%.

This is the necessary sample for the bivariable association but, as our study has 5 different cohorts depending on the maternal ethnicity (Caucasian, Asiatic, Maghreb, Black African and Others) we will need 160 exposed subjects of each ethnicity but also 480 subjects non exposed of every ethnicity, making a total of 3200 subjects.

At the Hospital Josep Trueta approximately 2450 children are born each year, and all pregnant women are screened in the first trimester. By analyzing the results of the last 3 years we will manage to have a sample great enough to ensure a statistically obvious difference (≈7350 newborns).

3.5 Variables. Data collection

EXPOSURE VARIABLES

- **PAPP-A and βhCG** → All pregnant women who accept the screening test of the first trimester have a blood sample collected in gestational week 11-13^{+6}. Maternal serum PAPP-A and βhCG is measured in our centre's laboratory using DELFIA Xpress time-resolved fluoroimmunoassay (Perkin- Elmer, Turku, Finland) – Picture II,III – and an ultrasound examination is carried out to measure nuchal thickness (NT) and crown-rump length (CRL) by a qualified Obstetrician using a Nemio XG TOSHIBA ® ultrasound machine.

  The PAPP-A and βhCG measured in absolute concentrations (ng/mL) are converted into multiples of the median (MoM) by dividing the absolute concentration with the median concentration at the specific gestational age (estimated by CRL in ultrasound examination with validated gestational age tables) and corrected for maternal age. The transformation of values is crucial as both glycoproteins change their serum levels during pregnancy.

  Data regarding the measures of PAPP-A and βhCG will be obtained through the LyfeCycle vs 3.2 Database of the Laboratory Department in Hospital Universitary Dr. Josep Trueta – Picture IV –, in which all the serum and ultrasound measures used in the first trimester screening test for chromosomal abnormalities are registered. Information will be downloaded into the *Access Office 2007® Microsoft®* database.

Low PAPP-A and free βhCG will be defined as <10th percentile from MoMs and we will calculate also the relative risk for <5th percentile.ç

- **Ethnicity**→ Defined as the human community having racial, religious, linguistic, and certain other traits in common. In Hospital Dr Josep Trueta ethnicity is always recorded in the first trimester ecography and classified according: Caucasian, Asiatic, Maghreb, Black African or Others.

OUTCOME VARIABLES

- **Intrauterine growth restriction (IUGR)** → Criteria for defining IUGR will be the recommended by the "Sociedad Española de Ginecología y Obstetricia" which is the one used in Hospital Dr Josep Trueta by all Obstetrics. IUGR is diagnosed on the basis of 3 criteria:
  1) A decrement of the estimated fetal weight to below the 10th percentile of a standard growth curve depending of gestational age, measured by abdominal circumference. This estimation is automatically calculated by the "Calculadora gestacional" v2013.1 Francesc Figueras. – Picture V–
  2) A Doppler pulsatility index of umbilical artery greater than the 90th percentile of our reference curve – Picture VI –
  3) A birthweight below the 10th percentile for the gestational age curve – Picture VII –

  We use these criteria to identify the subgroup of SGA foetuses with true IUGR associated with placental dysfunction. Women will be assigned in two groups. Normal pregnancy group is defined as those pregnancies in which a life baby was delivered after 37 complete gestational weeks with birth weight at or above the 10th percentile for gestational age and sex. The IUGR group differs in that the birth weight is below the 10th percentile; there is a decrement of estimated fetal weight to below the 10th percentile and the Doppler pulsatility index of umbilical artery greater than the 90th percentile. Database will be obtained from SAP Gui for Windows Database.

COVARIABLES

- **Maternal age** → Measured in years at conception (Mean ± SD)
- **Maternal weight** → Measured in kilograms (Mean ± SD)
- **Maternal size** → Measured in centimetres (Mean ± SD)
- **Smoking**→ Yes/ No
- **Gestational age** → Days (Mean ±SD)
- **Maternal diabetes** → Yes/ no
- **Parity** → Primiparous/ Multiparous
- **Mean CRL at ultrasound** → Cm (mean ± SD)

4. STATYSTICAL ANALYSIS

First, a baseline table will be done with the characteristics of the study population with the number and percentage of each variable that we have registered. – Table 1 –

Second, a bivariate analysis will be performed using the Chi^2 test of association and the proportions will be presented by absolute numbers and percentages. Moreover, the Relative Risk (RR) will be calculated for each group. The independent variable will always consist of two categorical components: the percentile of the marker and ethnicity, and the dependent variable is the presence or absence of IUGR diagnosed by the actual criteria. A confidence interval of 95% will be assumed and we will consider p value <0, 05 to consider that there is a significance difference. – Table 2 and 3 –

Finally, a Poisson regression will be performed in order to add all the co variables that could skew the main association we want to analyse. With continuous variables, if we can assume a normal distribution, we will estimate the mean and standard deviation and, if we cannot assume it we will estimate the median, first and third quartile. For categorical variables overall percentages will be estimated.

All analyses will be performed using Statistical Package for the Social Sciences (SPSS Statistics, ver. 18)

5. ETHICAL CONSIDERATIONS

All women included in the database signed an informed consent so as to perform the first trimester screening test – Annex 2 –

The principle of the World Health Association *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects* (Assamblea General, Fortaleza, Brazil, October 2013), will be followed in the current study.

According to "*Ley Orgánica 15/1999, 13 de Diciembre,Protección de Datos de Carácter Personal",* clinical history information, names and surnames will remain anonymous when collecting data from the database and publishing results.

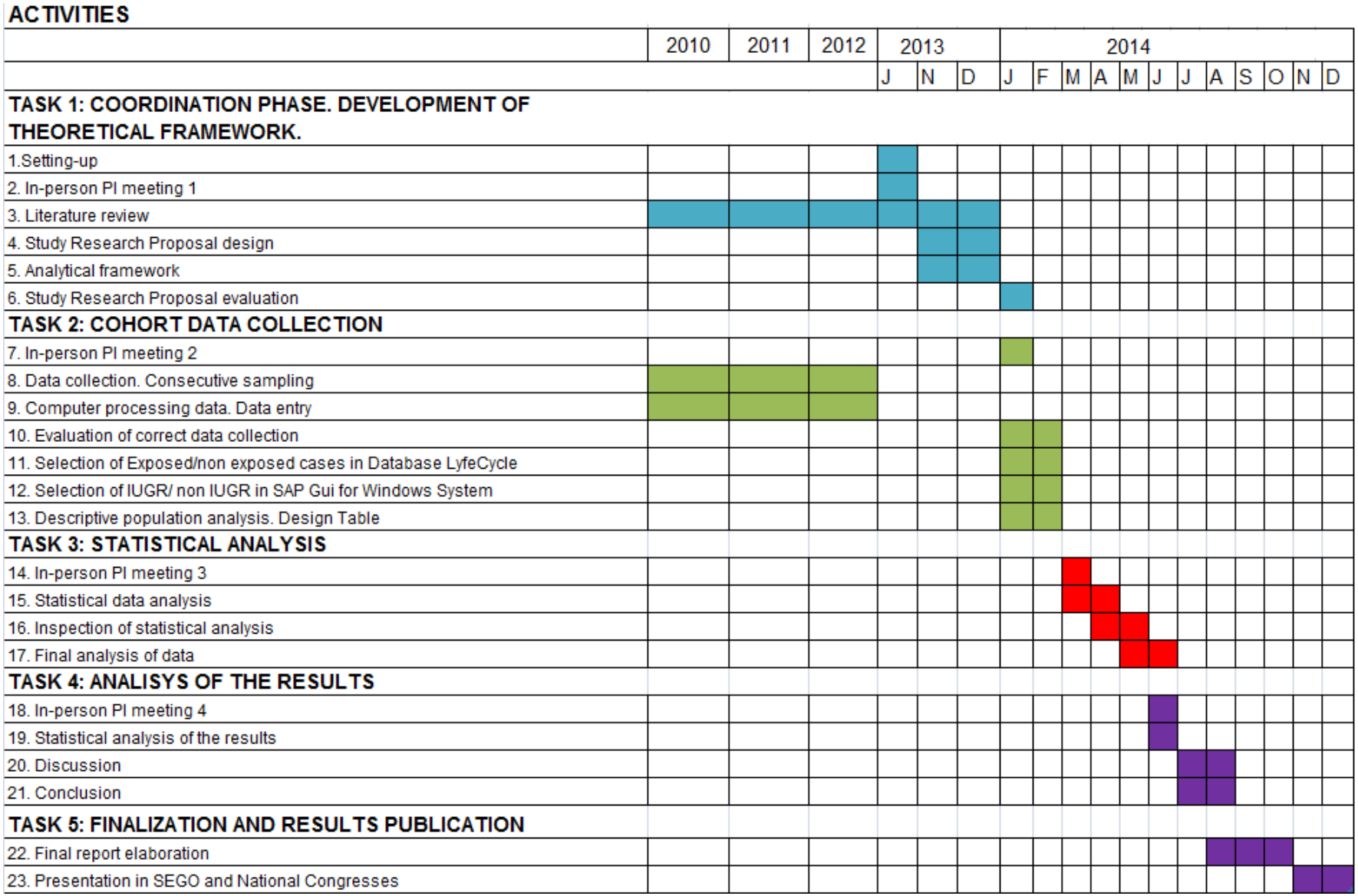
This protocol will be sent to the CEIC Department (Comitè Etic de Investigació Clínica) of The Hospital Universitari Josep Trueta, in order to be evaluated and accepted.

6. LIMITATIONS OF THE STUDY

The main limitation we have in the research we propose is confusing bias. The own characteristics of the pregnant women and previous medical history could have confounding effects on the study results and become conflicting. For this reason, we have collected as much co variables as possible that could skew the main variables we want to make the association (levels of PAPP-A, βhCG and ethnicity). These co variables are collected systematically by Obstetrics in the first trimester aneuploidy screening so as to calculate the risk. Poisson regression will include all co variables in order to adjust the Relative Risk as much as possible to our main variables.

Another limitation of the study is the difficulty of the categorization of ethnicity by the clinician. The group “Others” comprises a wide variety of interpretations and results can be slanted as the measure of this variable is not accurate enough. Moreover, if we find differences between ethnicities, it could be not only for this but also for the place inhabited, the quantity or quality of nourishment, socioeconomic status, etc.

7. STUDY CHRONOGRAM



ACTIVITY	DEPENDANT
1. Setting up	All the Research Team of Gyn. and Obstetrics Department of the Hospital and Principal Project Investigators
2,7,14,18. In person PI meetings	Principal Project Investigators
3. Literature review	All research team
4. Study research and proposal design	Principal project investigators
5. Analytical framework	Principal Project Investigators
6. Study research proposal evaluation	CEIC (Comitè d'Ètica i Investigació Clínica)
8. Data collection. Consecutive sampling	All Gyneacologists team when women attend to first trimester screening and in chillbirth.
9. Computer processing data	All Gyneacologists team when women attend to first trimester screening and in chillbirth.
10. Evaluation of correct data collection	Head of Gyneacology and Obstetrics Department
11. Selection of exposed/Non exposed cases in Database Lifecycle	Principal project investigators
12. Selection of IUGR/non IUGR in SAP Gui for Windows Database	Principal project investigators
13. Descriptive population analysis.	Principal project investigators
15.Statistical data analysis	Statistician
16. Inspection of statistical analysis	Head of Gyneacology and Obstetrics Department
17. Final analysis of data	Statistician
19. Analysis of results	All research team
20. Discussion	All research team
21. Conclusion	All research team
22. Article publication	Publication Department
23. Presentation to SEGO (Soc. Española de Ginecología y Obstetricia) and National Congresses	All research team

8. BUDGET

ITEM	QUANTITY	COST (€)	TOTAL
Literature review. Library expenses: - Payment articles and other literature material	10units	30€	300€
Staff working - Hire a Statistical Expert for data analysis	1person/ 30hours	35€/h	1050€
Material expenses - Printing and paper packs	5u	20€	100€
Publication costs - International journal of Gyneacology and Obstetrics	--	3000€	3000€
Presentation costs - Presentation to SEGO - Presentation to a National Professional Congress	-- --	1500€ 1500€	1500€ 1500€
Meeting-travelling expenses - Transport (AVE Bcn-Madrid) - Accommodation - Food and miscellanea	4 people 4 people 4 people	≈85,50€ ≈60€ ≈ 100€	≈342€ ≈240€ ≈400€
TOTAL	--	--	**8432 €**

9. CLINICAL AND HEALTHCARE IMPACT

With this project we wish to achieve more information about the possible further values of the two biomarkers PAPP-A and βhCG, which nowadays are primarily used in the first trimester screening, together with the nuchal translucency (NT), for the assessment of chromosomal abnormalities. Finding a new application for these markers would be only beneficial as they are performed by routine to all pregnant women.

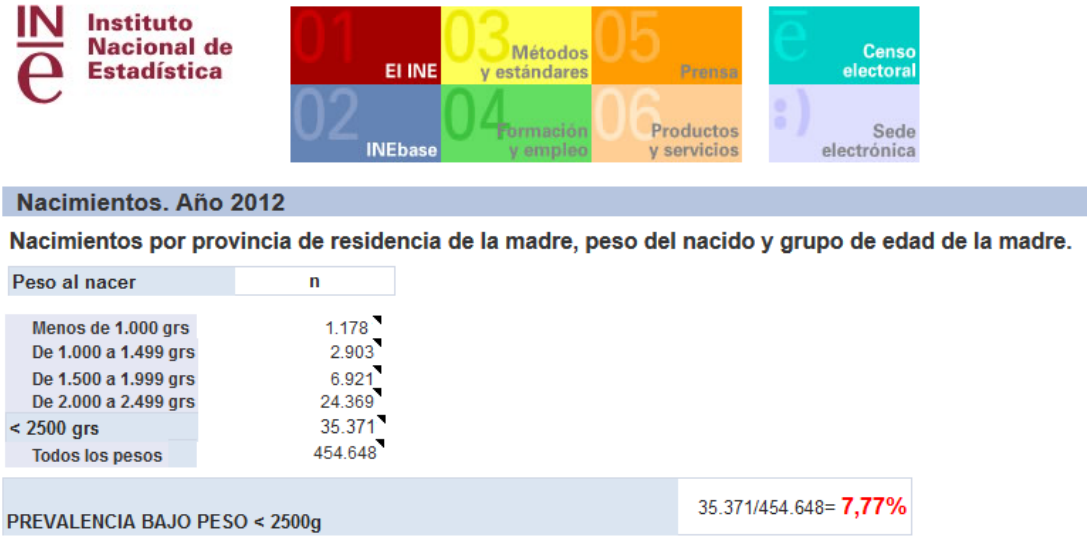
We would like to know if these markers in association with maternal ethnicity feature can help identifying women at risk of Intrauterine Growth Restriction. If the results show an association with a high predictability it would be reasonable to consider the possibility to perform increased surveillance for these high risk pregnancies, or maybe offer treatment interventions in early pregnancy, if more research is done in this field. We also believe that if this work is published in SEGO (Soc. Española de Ginecología y Obstetricia) and presented to several National Congresses it will provide information and inspiration for further studies. If we manage to identify this condition in early pregnancy many more studies would like to invest about possible curative treatments from early weeks of gestation.

Actually, this condition is the 2nd leading neonatal mortality and involves a large numbers of complications not only at short-term but also at long term. If we can follow more closely these patients we might reduce in the long term perinatal mortality and morbidity due to this adverse outcome. Besides, this would mean a reduction in the cost of length of stay in the Hospital, neonatal intensive unit and additional treatments.

Finally, we hope this project will bring increased knowledge about mechanisms of Intrauterine Growth Restriction, since there is so little knowledge of its physiopathology.

10. TABLES, FIGURES AND PICTURES

Picture I: **Instituto Nacional de Estadística (www.ine.es). Prevalence of low birth weight in Spain.**



Nacimientos. Año 2012

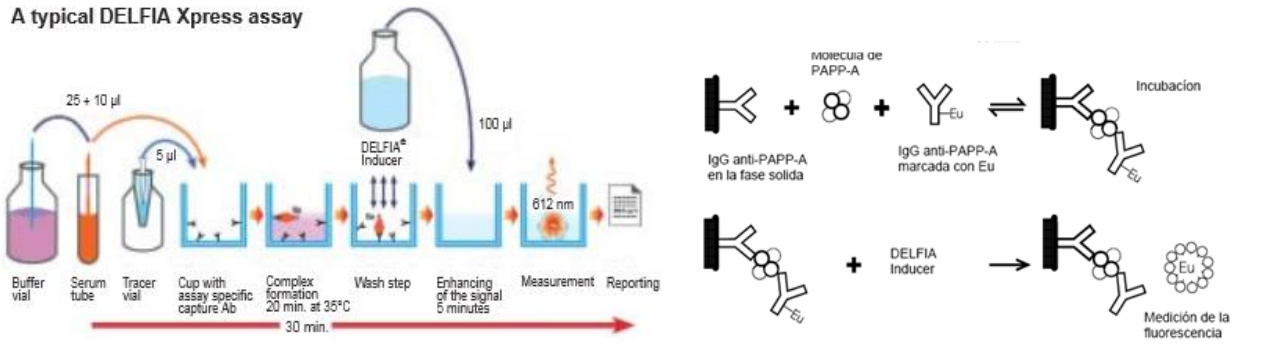
Nacimientos por provincia de residencia de la madre, peso del nacido y grupo de edad de la madre.

Peso al nacer	n
Menos de 1.000 grs	1.178
De 1.000 a 1.499 grs	2.903
De 1.500 a 1.999 grs	6.921
De 2.000 a 2.499 grs	24.369
< 2500 grs	35.371
Todos los pesos	454.648

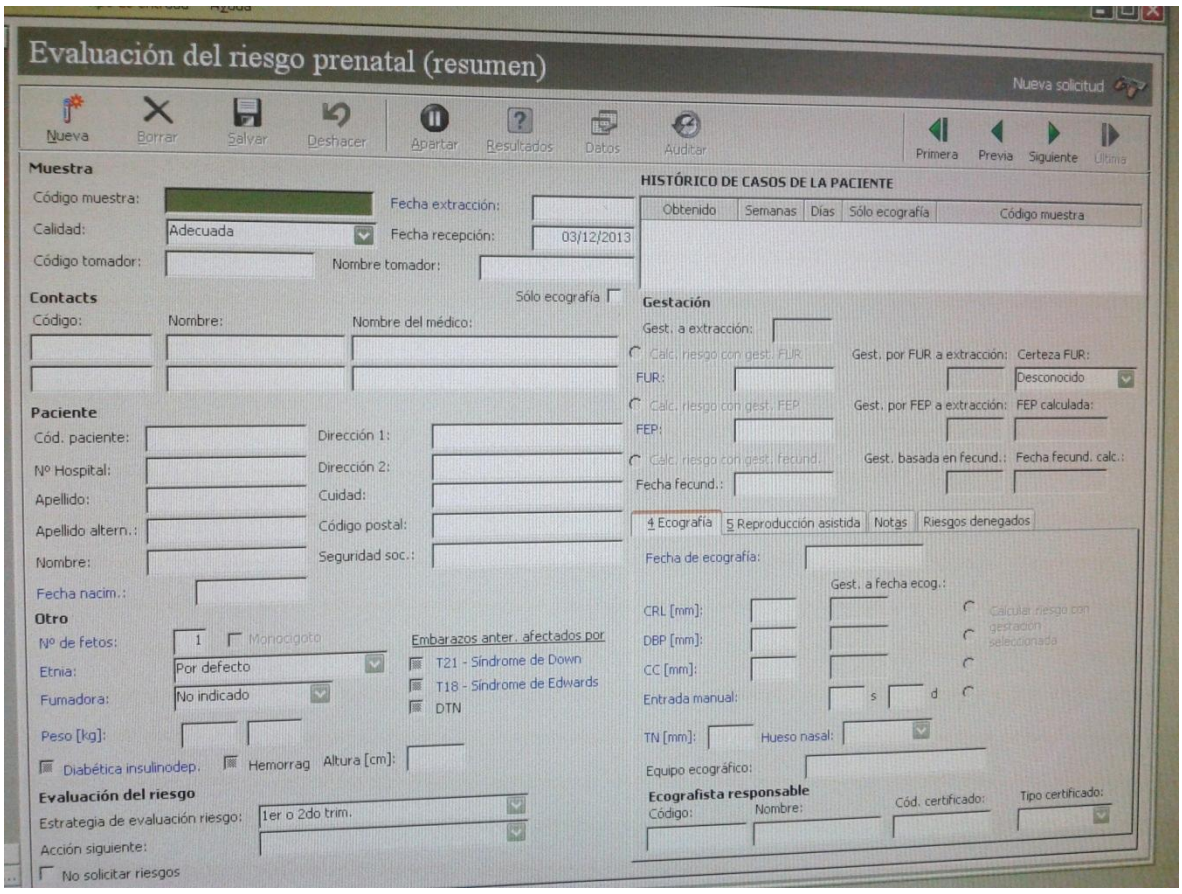
PREVALENCIA BAJO PESO < 2500g	35.371/454.648= **7,77%**

Picture II: **DELFIA Xpress time-resolved fluoroimmunoassay (Perkin- Elmer, Turku, Finland) from Hospital Dr Josep Trueta Laboratory.**

Picture III: **The DELFIA Xpress assay is a solid phase two-site fluorometric assay based on the direct sandwich technique in which two monoclonal antibodies (derived from mice) are directed against two separated antigenic determinants on the PAPP-A/ βhCG molecule. The DELFIA inducer dissociates europium ions from the labelled antibodies into the solution where they form highly fluorescent chelates and which is proportional to the concentration of PAPP-A or β hCG (mU/L).**

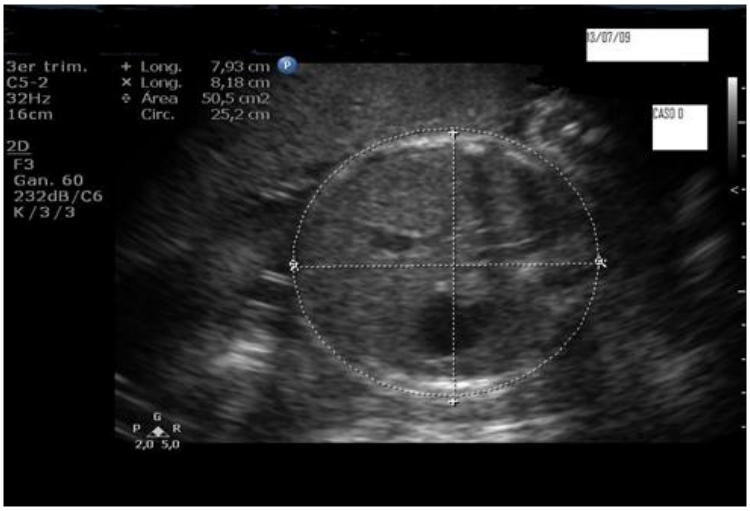


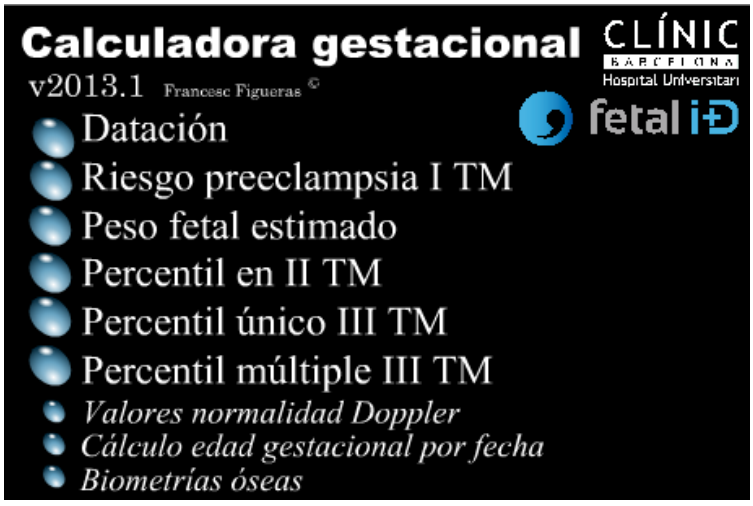
Picture IV: **LifeCycle database 3.2 for Prenatal Screening with Elipse Screening Engine from Hos pital Dr Josep Trueta Laboratory.**



Picture V: **Left: Spanish reference table abdominal perimeter by gestational age used in Hospital Materno-Infantil Vall d'Hebron and in Hospital Dr Josep Trueta. Top right: Measurement of Abdominal circumference by ultrasound in Hospital Dr Josep Trueta. Bottom right: Estimated fetal weight is calculated automatically by the "Calculadora gestacional" v2013.1 from Francesc Figueras system.**

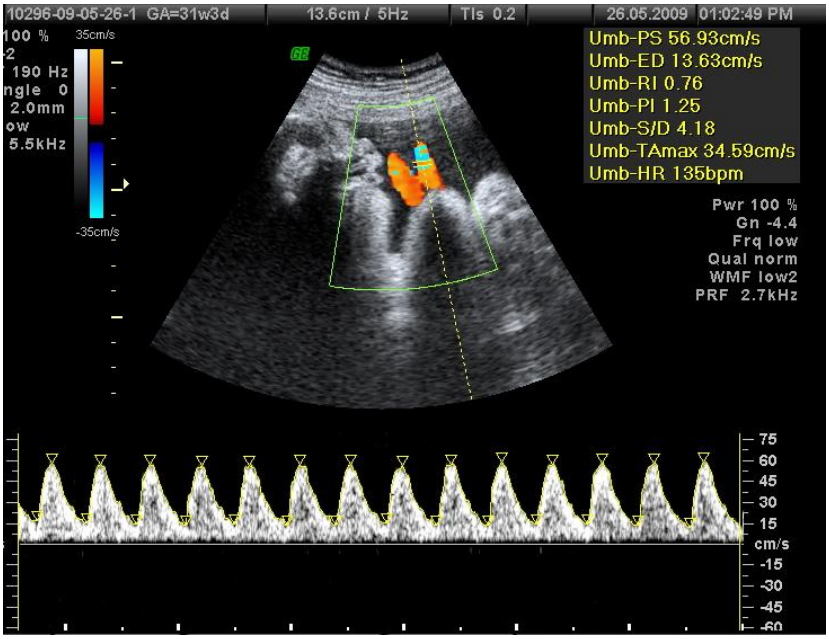
Circunferencia Abdominal (CA)			
Semana	P5 (mm)	P50 (mm)	P95 (mm)
16	85	95	105
17	96	107	118
18	108	118	128
19	118	130	142
20	128	141	154
21	134	152	165
22	150	164	178
23	160	175	190
24	170	187	204
25	181	199	217
26	192	211	230
27	202	222	242
28	212	233	254
29	228	245	262
30	236	254	272
31	246	264	282
32	254	274	294
33	262	282	302
34	270	292	314
35	280	302	324
36	288	310	332
37	296	318	340
38	302	326	350
39	308	332	356
40	310	336	362
41	314	340	366





Picture VI: **Left: Spanish reference table pulsatility index of umbilical artery used in Hospital Materno-Infantil Vall d'Hebron and in Hospital Dr Josep Trueta (Arduini D J Perinat Med 1990; 18:165). Right: Doppler ultrasound of umbilical artery.**

EG (s)	IPAU (p95)[1]
20	2,01
21	1,96
22	1,9
23	1,85
24	1,79
25	1,73
26	1,69
27	1,64
28	1,6
29	1,58
30	1,54
31	1,5
32	1,48
33	1,46
34	1,43
35	1,42
36	1,41
37	1,4
38	1,4
39	1,4
40	1,4



Picture VII: **Santamaría R. Spanish neonatal weight tables according to gestational age. En: S.A.M, ed 1998. Used in Hospital Materno-infantil Vall d'Hebrón and in Hospital Dr Josep Trueta.**

Embarazo único sin diferenciar por sexo. Distribución percentilar

Semanas	3	5	10	25	50	75	90	95	97
26	670	670	690	763	850	975	1070	1125	1125
27	715	715	720	775	923	1063	1125	1170	1170
28	730	750	750	850	1100	1225	1510	1530	1600
29	845	845	850	975	1165	1385	1570	2470	2470
30	970	990	1010	1180	1365	1580	2100	3135	3220
31	1140	1160	1245	1400	1610	1970	2225	3100	3250
32	1160	1195	1250	1525	1833	2050	2385	2670	2940
33	1150	1300	1470	1750	1950	2200	2300	2425	2450
34	1300	1410	1625	1975	2200	2530	2810	2950	3075
35	1600	1745	1930	2180	2445	2700	2995	3205	3350
36	1750	1840	2050	2340	2600	2883	3200	3350	3470
37	2100	2200	2350	2600	2870	3130	3400	3555	3700
38	2300	2400	2550	2800	3050	3300	3550	3750	3860
39	2500	2550	2700	2910	3170	3440	3700	3850	3950
40	2600	2680	2800	3020	3270	3540	3800	3950	4040
41	2650	2740	2870	3100	3370	3650	3900	4050	4160
42	2640	2715	2880	3145	3400	3680	3945	4110	4220
43	2650	2710	2790	3000	3240	3550	3880	4020	4130

Table I: Baseline characteristics of the study population

Characteristics	n=	%
Mean maternal age (years)		__
Mean maternal weight (kg)		__
Mean CRL at ultrasound (mm)		__
Mean bHCG level		__
Mean PAPP-A level		__
Maternal ethnicity		
• Caucasian		
• Maghreb		
• Asiatic		
• Black african		
• Other		
Maternal smoking		
Maternal diabetes		
Mean birthweight (gr)		
IUGR fetuses		

Table 2: Low PAPP-A as predictive of IUGR by ethnicity

PAPP-A as predictive of IUGR

Variable		IUGR	Non- IUGR	RR (95% CI)	p value
Caucasian	PAPP-A <5th p				
	PAPP-A <10th p				
	PAPP-A >10th p			Reference	__
Asiatic	PAPP-A <5th p				
	PAPP-A <10th p				
	PAPP-A >10th p			Reference	__
Maghreb	PAPP-A <5th p				
	PAPP-A <10th p				
	PAPP-A >10th p			Reference	__
Black	PAPP-A <5th p				

Affrican					
	PAPP-A <10th p				
	PAPP-A >10th p			Reference	__
Other	PAPP-A <5th p				
	PAPP-A <10th p				
	PAPP-A >10th p			Reference	__

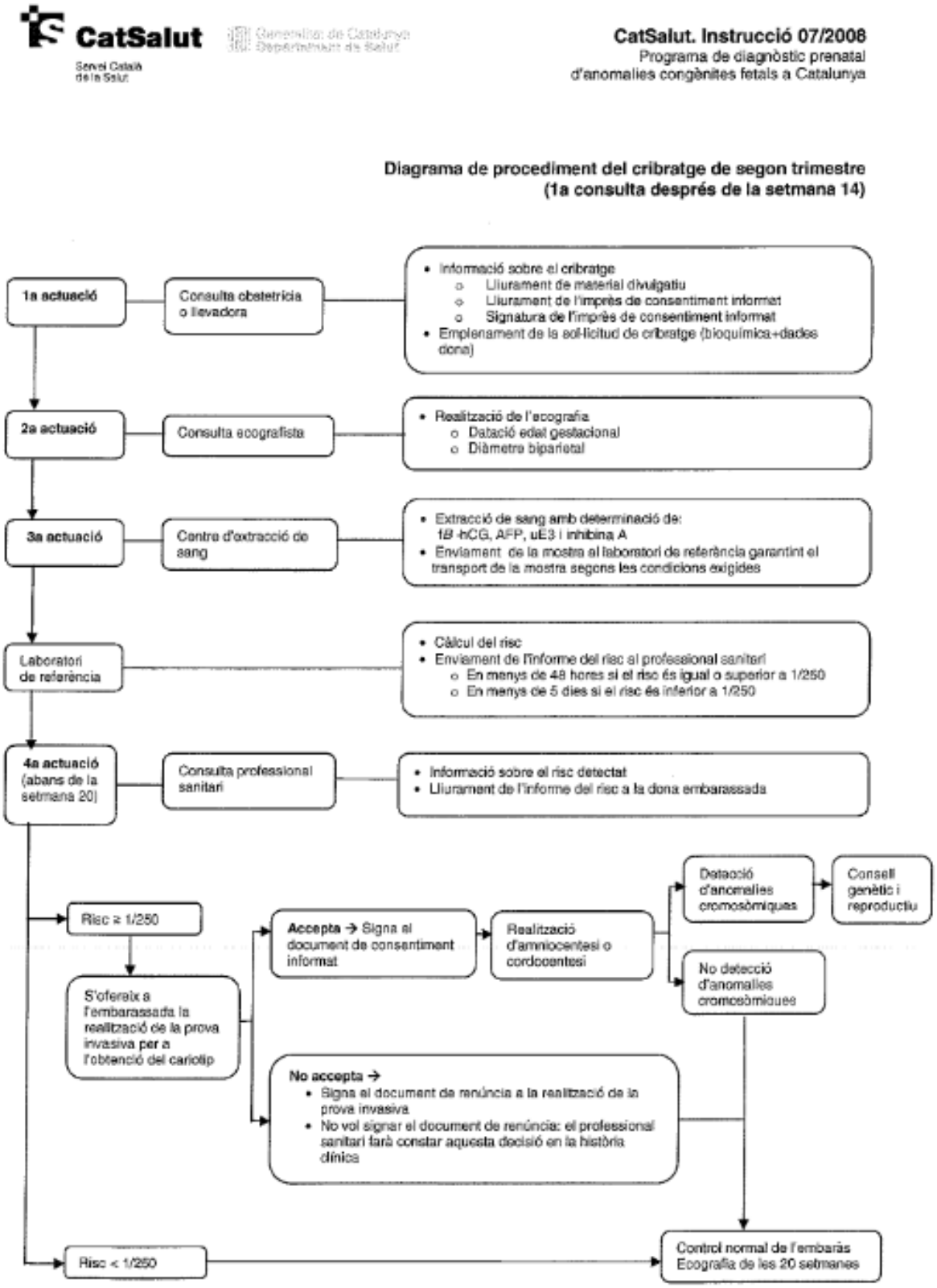
Table 3: Low β as predictive of IUGR by ethnicity

βhCG as predictive of IUGR

Variable		IUGR	Non- IUGR	RR (95% CI)	p value
Caucasian	βhCG <5th p				
	βhCG <10th p				
	βhCG >10th p			Reference	__
Asiatic	βhCG <5th p				
	βhCG <10th p				
	βhCG >10th p			Reference	__
Maghreb	βhCG <5th p				
	βhCG <10th p				
	βhCG >10th p			Reference	__
Black African	βhCG <5th p				
	βhCG <10th p				
	βhCG >10th p			Reference	__
Other	βhCG <5th p				
	βhCG <10th p				
	βhCG >10th p			Reference	__

11. ANNEX

Annex 1: "Programa de diagnòstic prenatal d'anomalíes congènites fetals a Catalunya"



Annex 2: First trimester screening informed consent of Hospital Dr Josep Trueta

CatSalut
Servei Català de la Salut

Generalitat de Catalunya
Departament de Salut

CatSalut. Instrucció 07/2008
Programa de diagnòstic prenatal d'anomalies congènites fetals a Catalunya

Sol·licitud de cribratge de primer trimestre

Sol·licitud de cribratge de primer trimestre

Dades de la gestant

Nom | 1r cognom | 2n cognom

CIP | Telèfon

Adreça | Municipi/localitat | Codi postal

Regió Sanitària de residència | Data de naixement | Nombre d'embarassos anteriors (fórmula obstètrica)

___ / ___ / ___ / ___
GT PP A FV

Classe social[1] | Nivell d'estudis[2]

Factors de correcció *(l'absència d'aquestes dades pot influir en el resultat final del risc calculat)*

Raça/ètnia

☐ blanca ☐ negra ☐ asiàtica ☐ altra *(especifiqueu-la):*

Pes | Consum de tabac

kg ☐ no ☐ sí *(especifiqueu el nombre aproximat de cigarrets/dia):*

Diabetis insulinodependent

☐ no ☐ sí, ben controlada ☐ sí, no controlada

Gestació prèvia amb malformacions

☐ no ☐ sí *(especifiqueu quina):*

Dades de la gestació

Gestació

☐ única ☐ doble, monocorial ☐ doble, bicorial ☐ desconeguda

Edat gestacional: setmanes de gestació segons DUR

Si la gestació és per reproducció assistida amb donació d'ovòcits, especifiqueu l'edat de la donadora d'ovòcits

anys

Dades ecogràfiques *(si s'ha realitzat l'ecografia en el moment de la sol·licitud)*

Cognoms i nom de l'ecografista | Telèfon de contacte

Data de l'ecografia | Longitud cefalocaudal (LCC) | Translucidesa nucal (TN)

mm | mm

Dades del metge/essa o llevador/a sol·licitant

Cognoms i nom | Núm. de col·legiat/ada | Telèfon de contacte

Centre sanitari

Signatura

Data

Centre d'extracció

Nom del centre d'extracció | Data de l'extracció

[1] Poseu-hi el número que correspongui:

1. Directives de l'Administració pública i d'empreses de 10 o més persones assalariades. Professions associades a titulacions de segon i tercer cicle universitari.
2. Directives d'empreses de menys de 10 persones assalariades. Professions associades a titulacions de primer cicle universitari. Tècniques i professionals de suport. Artistes i esportistes.
3. Administratives i professionals de suport a la gestió administrativa i financera. Treballadores dels serveis personals i de seguretat. Treballadores per compte d'altri. Supervisores de treballadors/es manuals.
4. Treballadores manuals qualificades.
5. Treballadores manuals semiqualificades.
6. Treballadores no qualificades.
7. Dones en atur.
8. Dones que treballen a casa.

[2] Poseu-hi el núm. que correspongui

1. No té estudis.
2. Estudis primaris.
3. Estudis secundaris de batxillerat.
4. Estudis secundaris de formació professional.
5. Estudis universitaris de grau mitjà (diplomatures).
6. Estudis universitaris de grau superior (llicenciatures).

Informe de cribratge de primer trimestre

Informe de cribratge de primer trimestre

Identificació del laboratori

Nom del centre (hospital, CAP, etc.) | Telèfon

Adreça | Municipi/localitat | Codi postal

Dades del metge/essa o llevador/a sol·licitant

Cognoms i nom | Centre de treball

Dades de la gestant

Cognoms i nom | CIP | Edat en la data prevista del part: anys

Raça/ètnia
☐ blanca ☐ negra ☐ asiàtica ☐ altra *(especifiqueu-la):*

Pes: kg | Gestació: ☐ única ☐ múltiple | Fumadora: ☐ no ☐ sí | Diabetis insulinodependent: ☐ no ☐ sí

Data de l'extracció | Edat gestacional el dia de l'extracció *(calculada a partir de l'LCC)*: setmanes dies

Data de l'ecografia | Edat gestacional el dia de l'ecografia: setmanes dies

Resultats

Nivell de β-hCG lliure en sèrum matern: ng/ml (MOM) | Nivell de PAPP-A en sèrum matern: UI/ml | Mesura de translucidesa nucal fetal: mm (MOM)

Altres comentaris, si s'escau

Risc de síndrome de Down: 1 entre | **Risc de síndrome d'Edwards**: 1 entre

Comentaris

Síndrome de Down
☐ baix risc ☐ es recomanen estudis addicionals

Síndrome d'Edwards
☐ baix risc ☐ es recomanen estudis addicionals

Altres comentaris, si escau

Signatura de la persona responsable

Data de l'informe *(Data de la còpia, si escau):*